Crystal Structure of the N-terminal Ankyrin Repeat Domain of Human RNase L

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Ribonuclease L (RNase L) is implicated in both the molecular mechanisms of interferon action and the fundamental control of RNA stability in mammalian cells. RNase L is catalytically active only after binding an unusual activator molecule containing a 5'-phosphorylated 2',5'-linked oligoadenylate, (pp)p(A2'p5')2A (2-5A), in the N-terminal half. RNase L consists of three domains, namely the N-terminal ankyrin repeat domain, the protein kinase homology domain, and the C-terminal ribonuclease domain. The N-terminal ankyrin repeat domain is responsible for 2-5A binding, and the C-terminal domain is responsible for catalytic activity.

We have determined the crystal structure of the N-terminal ankyrin repeat domain (ANK) of human RNase L complexed with the activator 2-5A at 1.8 Å resolution [1]. The ANK folds into eight ankyrin repeat elements and forms an extended curved structure with a concave surface. The 2-5A molecule is accommodated in the concavity and interacts with ankyrin repeats 2 to 4. Two structurally equivalent 2-5A binding motifs are found at repeats 2 and 4. The structural basis for 2-5A recognition by ANK is essential for designing stable 2-5As with a high likelihood of activating RNase L.

[1] Tanaka N., Nakanishi M., Kusakabe Y., Goto Y., Kitade Y., Nakamura K.T., *EMBO J.*, 2004, **23**, 3929.

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